REMARKS

Claims 1-85 were pending. Claims 1-58, 61, 66-76 and 78-83 and 85 are cancelled without prejudice to Applicants' right to prosecute their subject matter in the present application and in related applications. Claims 59, 60, 62, 63, 77 and 84 are amended without any intent of disclaiming equivalents thereof. New claims 86-94 are added. Accordingly, upon entry of this paper, claims 59, 60, 62-65, 77, 84 and 86-94 are pending and presented for consideration.

Claim amendments

Claim 59 is amended to further clarify steps involved in Applicants' claimed method of identifying a target of a perturbation to a biological system using a pre-determined quantitative model. Support for the amendments can be found throughout the specification as originally filed, for example, from paragraph 0204 to paragraph 0214, and from paragraph 0227 to paragraph 0233 and the Examples section (e.g., Example 4). The paragraph numbers used herein are based on the paragraph numbering used in the original PCT application as published, WO 03/077062.

Claim 60 is amended to specify that the perturbation is a small molecule compound. Support for the amendment can be found in the specification as originally filed, for example, in paragraph 0228.

Claims 62, 77 and 84 are amended for clarification and consistency. Claim 84 is also amended to clarify that the computer-readable medium is "non-transitory." Support for this amendment can be found in Figure 9.

Exemplary support for new claims 86-94 is shown as follows.

New Claims	Exemplary Support
86	Original claim 52; .
87	Paragraph 0217; Example 1.
88	Paragraph 0218; Example 3.
89	Paragraphs 0243 and 0244.
90	Paragraph 0028.

91	Paragraph 0028; and the Examples section
92	Paragraph 0124.
93	Example 1.
94	Example 4.

Applicants respectfully submit that no new matter is introduced by the claim amendments.

Telephonic Interview

Applicants thank Examiner Riggs for the telephonic interview conducted on May 27, 2010, with Fangli Chen, James Collins, Diego di Bernardo and Timothy Gardner.

During the interview, Applicants presented to Examiner Riggs the distinctions between Applicants' claimed method and the prior art method disclosed in Stoughton. In particular, Applicants pointed out that Applicants' claimed method requires identifying a target of a perturbation to a biological system using a pre-determined quantitative model of the biological system, which cannot be done by the prior art method based on a qualitative binary matrix. Examiner Riggs indicated that this distinction is helpful to overcome the obviousness rejection under 35 USC §103, and suggested that Applicants present nonobviousness arguments based on this distinction in a written response. Examiner Riggs also suggested certain claim language to more specifically define the claimed invention.

Applicants thank Examiner Riggs for a productive interview. Applicants have incorporated the Examiners' suggestions in this response.

Objection to the specification

The specification is objected to because it contains embedded hyperlinks and/or other forms of browser-executable code on pages 87, 115, 253, 301 and 307. Applicants have amended the specification to delete any hyperlinks or other forms of browser-executable code

(see Amendments to the Specification). Applicants therefore respectfully request this objection be withdrawn.

Claim rejections under 35 U.S.C. §112, second paragraph

Claims 59-65, 77 and 84 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Office Action indicated that the limitation "determining the response of at least one of the biochemical species in the biological network to the compound" lacks antecedent basis. Applicants have amended claim 59 to delete this limitation.

The Office Action also indicated that the limitation "calculating predicted perturbations of biochemical species in the biological network that would be expected to yield the determined responses according to the model" recited in claim 59 is unclear. Applicants have amended claim 59 to delete this limitation and specifically recite "calculating predicted perturbations to individual species that would yield the same response characterized at step (b) using a computer device having a software component suitably programmed to carry out such calculation using a pre-determined quantitative model of the biological system, wherein the predicted perturbations are calculated by determining predicted changes of expression or activity of individual species."

In addition, the Office Action alleged that the limitation "calculating predicted perturbations of biochemical species in the biological network that would be expected to yield the determined responses according to the model" is unclear. Applicants have amended claims 77 and 84 to specifically recite "calculate predicted perturbations to individual species in the biological system that would yield the response of step (ii) according to the model of the biological system."

Accordingly, Applicants respectfully submit that the amended claims fully comply with 35 U.S.C. §112, second paragraph, and request the rejections be reconsidered and withdrawn.

Claim rejections under 35 U.S.C. §101

Claims 59-65 are rejected under 35 U.S.C. §101 for being allegedly directed to non-statutory subject matter. According to the Office action, the claims neither recite or inherently involve any transformation of an article nor tie the recited process to any particular machine or apparatus. See, the Office Action, page 5.

Without acquiescing to the rejection, and solely to advance prosecution, Applicants have amended independent claim 59 to recite steps of "(a) perturbing a biological system comprising a plurality of biological species" and "(b) characterizing a response of the biological system to the perturbation by determining quantitative changes of expression or activity of the plurality of the biological species at steady state following the perturbation." Applicants submit perturbing a biological system clearly involves a transformation of an article, in this case, a biological system comprising a plurality of biological species, into a different state, which can be characterized by determining quantitative changes of expression or activity of the plurality of the biological species at steady state following the perturbation. Applicants further submit that the recited perturbing step is not merely an insignificant extra-solution step. In fact, the claimed method relates to identifying a target of perturbation; therefore, the step of perturbing the biological system is *central* to the solution because the perturbing step directly impacts the process of identifying the target. Therefore, Applicants submit that amended claim 59 clearly satisfies the transformation test set forth in *Bilski*.

In addition, Applicants have amended claim 59 to recite "calculating predicted perturbations to individual species that would yield the same response characterized at step (b) using a computer device having a software component suitably programmed to carry out such calculation using a pre-determined quantitative model of the biological system, wherein the predicted perturbations are calculated by determining predicted changes of expression or activity of individual species" which clearly ties the claimed process into a particular machine, i.e., a computer device that has a particular software component suitably programmed to carry out calculation of predicted perturbations to individual species using a pre-determined quantitative

model of the biological system. Applicants submit that the recited computer device is a *particular* machine and *not* a general purpose computer, or a nominal or token recitation that does not imparts meaningful limits on the claim scope, because the claimed process requires a particularly programmed computer device to carry out calculations of predicted perturbations using a pre-determined quantitative model, which clearly can not be performed by any computer or means. For example, Applicants' claimed process can not be performed by those computer devices that can only read *qualitative* models, which were commonly used in the field of network biology (see, Stoughton, the primary reference cited in the Office Action). Therefore, Applicants submit that amended claim 59 also satisfies the machine test set forth in *Bilski* because it clearly ties into a particular computer device that imparts meaningful limits on the claim's scope.

In view of the above, Applicants respectfully submit that independent claim 59 and its dependent claims clearly satisfy the *Bilski* test because the amended claims recite a process that transforms a particular article into a different state *and* also ties to a particular machine. Accordingly, Applicants respectfully submit the rejection under 35 U.S.C. §101 be reconsidered and withdrawn.

Claim rejections under 35 U.S.C. §103

Claims 59-63, 77 and 84 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Stoughton (U.S. Patent No. 6,132,969) in view of Lew (J. Clin. Invest. 1991, 87, 100-112). Claims 59-64, 77 and 84 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Stoughton in view of Lew and in further view of Wannenburg *et al.* (Am. J. Physiol. Heart Cir. Physiol., 2000, 279, H779-H790). Claims 59-63, 65, 77 and 84 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Stoughton in view of Lew and in further view of Scheidt et al. (J. Neurophysiol. 2001, 86, 971-985). See, the Office Action, pages 6-11. Applicants traverse the rejections for the reasons enumerated below.

Independent claim 59, as amended, recites the following:

59. A method of identifying a target of a perturbation comprising steps of:

(a) perturbing a biological system comprising a plurality of biological species;

(b) characterizing a response of the biological system to the perturbation by determining *quantitative* changes of expression or activity of the plurality of the biological species at steady state following the perturbation;

(c) calculating predicted perturbations to individual species that would yield the same response characterized at step (b) using a computer device having a software component suitably programmed to carry out such calculation using a pre-determined *quantitative* model of the biological system, wherein the predicted perturbations are calculated by determining predicted changes of expression or activity of individual species; and

(d) identifying an individual species as a target of the perturbation if the predicted perturbation to said individual species calculated at step (c) meets a predefined criterion.

[Emphasis added.]

Thus, amended claim 59 is directed to identifying a target of a perturbation by, *inter alia*, calculating predicted perturbations to individual species that would yield the same response caused by the perturbation using a pre-determined *quantitative* model of the biological system, wherein the predicted perturbations are calculated by determining predicted changes of expression or activity of individual species, and identifying an individual species as a target of the perturbation if the predicted perturbation to said individual species calculated at step (c) meets a predefined criterion. In other words, Applicants' claimed method requires a step of using a *quantitative* model to predict *quantitative* changes of expression or activity of individual species that would yield the same response by the perturbation. Applicants further submit none of the cited prior art references can render Applicants' claimed method obvious.

For example, the primary reference Stoughton teaches a *qualitative* Boolean network model, in which "the values of modifications or perturbations to cellular constituents input to a network are represented by binary quantities, conventionally signified by the values '0' and '1'." Stoughton, column 7, lines 50-55. Therefore, the Stoughton model can not be used to predict *quantitative* changes of expression or activity of individual species in a biological system, as

required by Applicants' claimed invention. The purpose of the Boolean network model taught by Stoughton is to identify the best set of experiments to identify the best predictive model and to determine an overall goodness of fit of the network model to a biological system. See, Stoughton, Abstract. In fact, Stoughton emphasized that it is fundamentally important to use only a coarse, discrete (often binary) abstraction and representation of the perturbations and changes. For example, Stoughton stated:

> Especially, the level of detail to which the network model reflects effects in the biological system is *important* in this invention. It is a *fundamental* discovery upon which this invention is based that, although in reality perturbations or modifications to input cellular constituents of a network and subsequent changes in other cellular constituents in the biological system are continuous, having a range of actual abundances or activities, *important and useful information on biological systems can be obtained with only a coarse, discrete (often binary) abstraction and representation of these perturbations and changes*.
>
> Accordingly, in this invention, the values of modifications or perturbations to cellular constituents input to a network are represented by *binary* quantities, conventionally signified by the values "0" and "1." In other words, perturbations or modifications are considered *for the purposes of this invention* to be either present or absent. . . .
>
> [Stoughton, column 7, lines 39-55. Emphasis added.]

Thus, Stoughton teaches away from a quantitative model, as required by Applicants' invention.

The secondary reference Lew does not cure the deficiencies of Stoughton. Lew discloses a mathematical model of the reticulocyte, seeking to explain how a cell with similar volume but much higher ionic traffic than the mature red cell regulate its volume, pH and ion content in physiological and abnormal conditions (abstract). Although Lew appears to use actual numerical values of variables (e.g., K^+, Cl^+, pH, etc.) in the reticulocyte model, Lew utilizes various graphs, each illustrating the relationship of two particular variables of the reticulocyte model (see, Figure 3, 4, 5 and 6). Lew is completely silent about perturbing a biological system, predicting *quantitative* changes of expression or activity of individual species using a pre-determined quantitative model that would yield the same response by the perturbation; and identifying an

individual species as a target of the perturbation if the predicted perturbation to said individual species meets a predefined criterion, as required by Applicants' method.

In addition, Applicants further submit that one skilled in the art at the time of the present invention, looking to improve Stoughton's method, would not have combined the Stoughton method with Lew because Stoughton made it clear that for its invention to work, it is fundamentally important to use discrete binary values instead of actual numerical details, to represent the perturbations and changes in a biological system. Therefore, Applicants submit that Stoughton and Lew can not be combined.

Neither of the remaining references, Scheidt and Wannenburg, cure the deficiencies in Stoughton and Lew. For example, Wannenburg tested the hypotheses that Ca^{2+} concentration and sarcomere length modulate force development via graded effects on cross-bridge kinetics in chemically permeabilized rat cardiac trabeculae. See, Wannenburg, Abstract. Scheidt studied how subjects learned to make movements against unpredictable perturbations. See, Scheidt, Abstract. Both Wannenburg and Scheidt are completely silent about identifying a target of a perturbation based on a quantitative model of a biological system.

Indeed, it is the present inventors who made quantitative analysis possible for complex biological systems. As discussed with the Examiner during the interview, Applicants' quantitative matrix uses continuously valued entries that can differentiate predicted changes of expression or activity among biological species. As a result, Applicants' claimed method is able to identify targets of a given perturbation by comparing the predicted changes to a pre-defined criterion (e.g., a pre-determined threshold), which cannot be done by prior art methods based on qualitative binary models. Indeed, prior to the present invention, no one has successfully used a biological network model to identify targets of exterior perturbations to a biological system. Therefore, the present invention represents a breakthrough in the field of system biology. Examples of successful identification of targets of pharmacological compounds (such as small molecules) using the present invention are provided in the specification (see, Example 4). This invention has been licensed to Gene Network Sciences, a biotech company which has successfully used it to identify drug targets and regulators for important biological pathways.

In view of the foregoing, Applicants submit the cited references, alone or in combination, can not render obvious Applicants' claimed invention. Applicants respectfully request the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

CONCLUSION

In view of the amendments and the arguments above, Applicants believe that all rejections have been overcome and the pending claims are in condition for allowance. The Examiner is invited to telephone the undersigned attorney to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,

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